

# Outcomes after late bone marrow and very early central nervous system relapse of childhood B-acute lymphoblastic leukemia: a report from the Children's Oncology Group phase III study AALL0433

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## Supplemental Data

### Supplemental Figure Legends

**Figure S1 Panel A & B:** Event-free survival (EFS) and Overall survival (OS) curves by minimal residual disease (MRD) range after induction-1, for late marrow relapse patients on standard arm (Arm A), with available MRD data (p-values < 0.0001). **Panel C & D:** EFS and OS curves by 0.1% MRD threshold after induction-1 for late marrow relapse patients on standard arm (Arm A), with available MRD data. The 3-year EFS and OS were  $85.1 \pm 4.6\%$  and  $95.1 \pm 2.8\%$  for patients with MRD <0.1%, and  $37.5 \pm 17.1\%$  and  $50.0 \pm 17.7\%$  for patients with MRD  $\geq 0.1\%$  (both p-values < 0.0001).

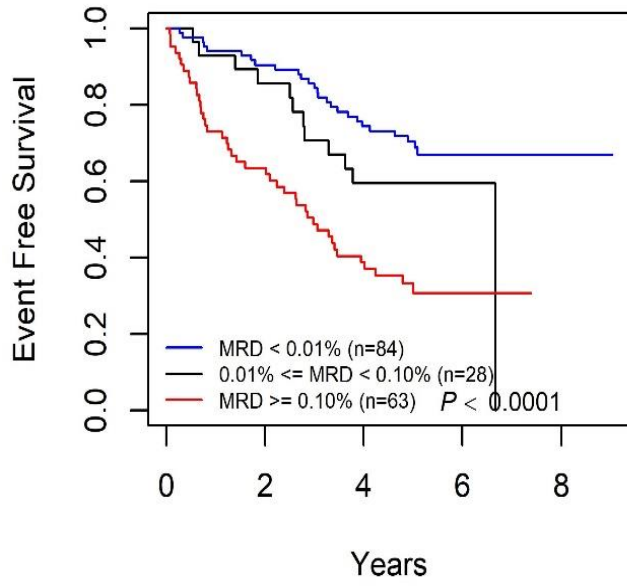
**Figure S2** Adjusted Disease-free survival (DFS) and Overall survival (OS) curves by hematopoietic cell transplantation (HCT) donor type for late marrow relapse patients. The 3-year adjusted DFS and OS were  $73.7 \pm 7.0\%$  and  $80.9 \pm 6.3\%$  for matched sibling donor, and  $72.0 \pm 9.2\%$  and  $72.0 \pm 9.2\%$  for other donors (p-values: 0.65 and 0.67).

**Figure S3** Adjusted Disease-free survival (DFS) and Overall survival (OS) curves by hematopoietic cell transplantation (HCT) vs. chemotherapy alone for patients with isolated CNS relapse. The 3-year adjusted DFS and OS were  $71.4\% \pm 17.0\%$  and  $71.4 \pm 17.1\%$  for HCT, and  $28.6\% \pm 9.9\%$  and  $42.9 \pm 10.8\%$  for chemotherapy alone (p-values: 0.12 and 0.18).

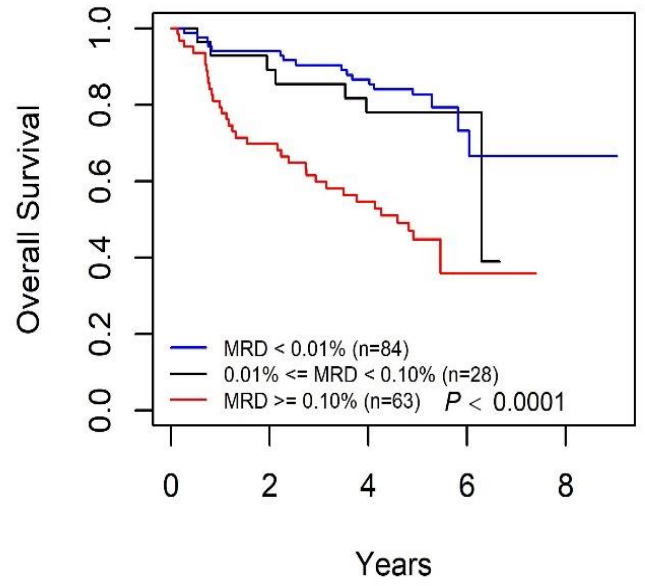
**Figure S4** Event-free survival (EFS) and Overall survival (OS) curves by Vincristine randomization for late marrow patients. The 3-year EFS and OS were  $70.1\% \pm 3.5\%$  and  $78.6\% \pm 3.1\%$  for Arm A, and  $55.1\% \pm 6.5\%$  and  $63.6\% \pm 6.3\%$  for Arm B, (p-values = 0.09 and 0.07).

Figure S1

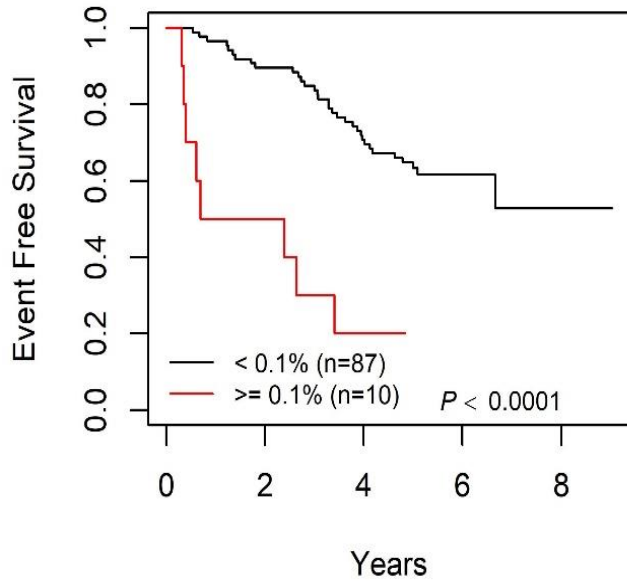
A



B



C



D

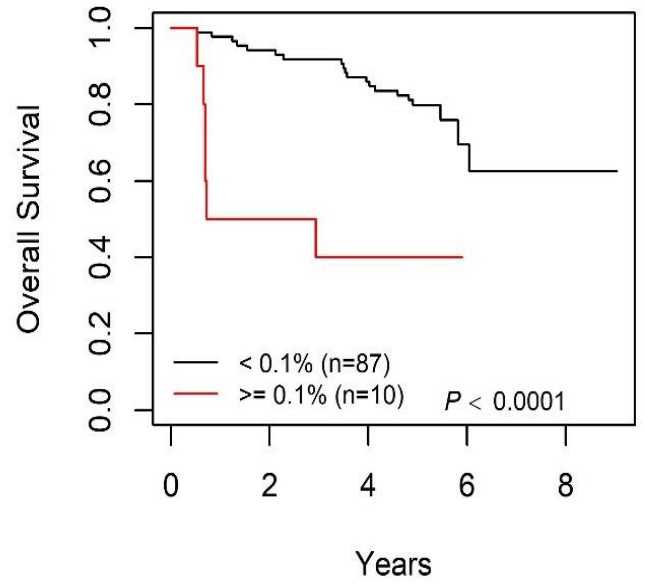
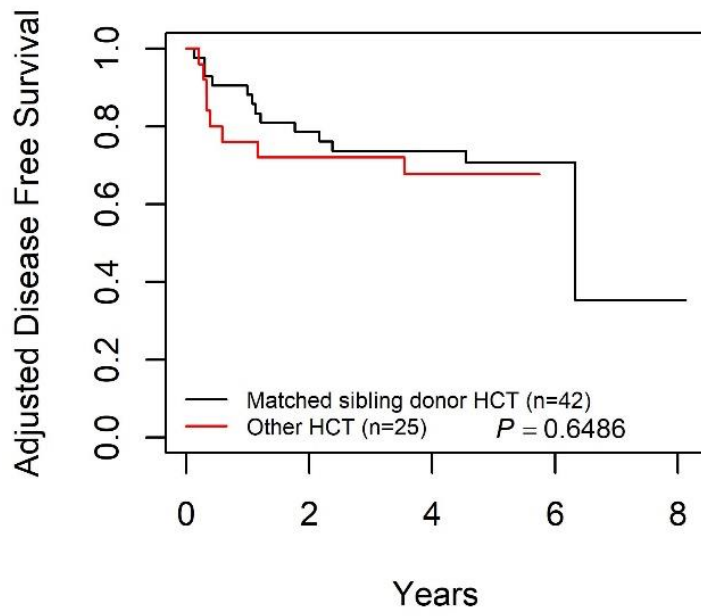
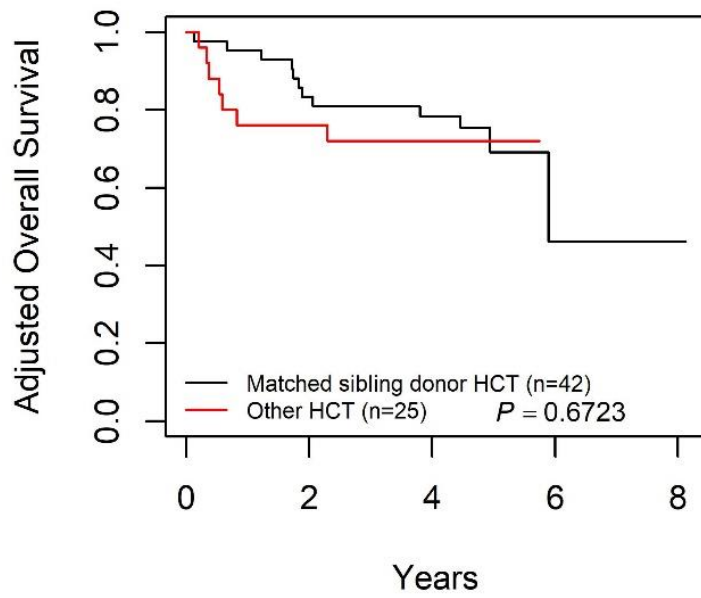


Figure S2

**A**

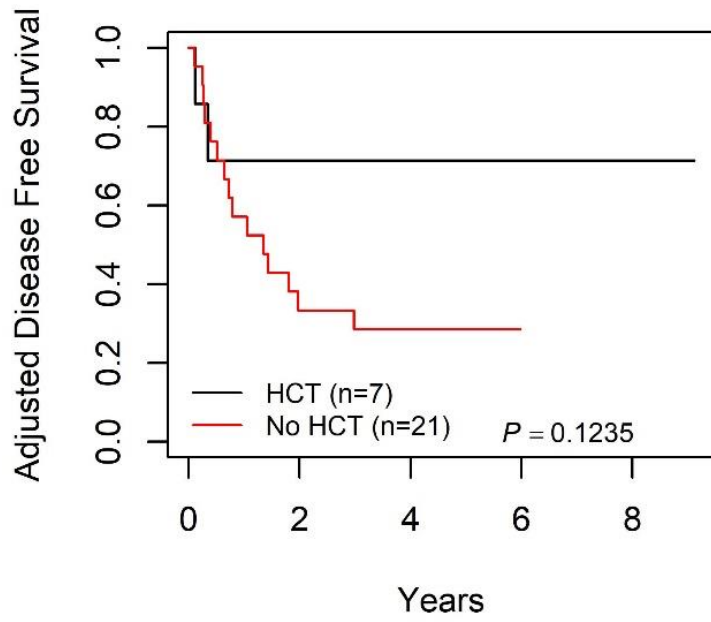


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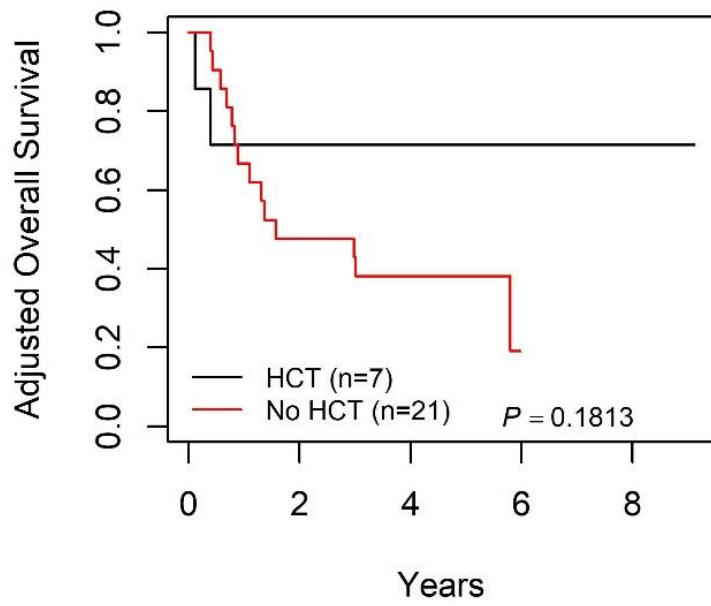


**Figure S3**

**A**

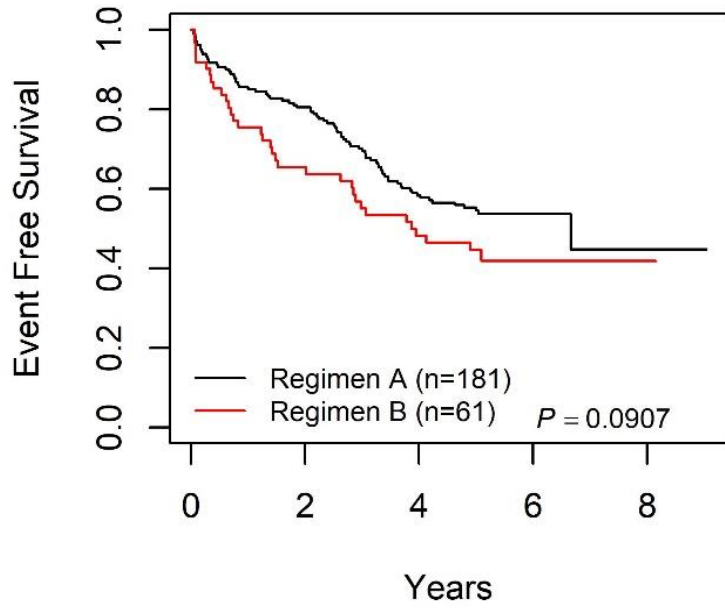


**B**

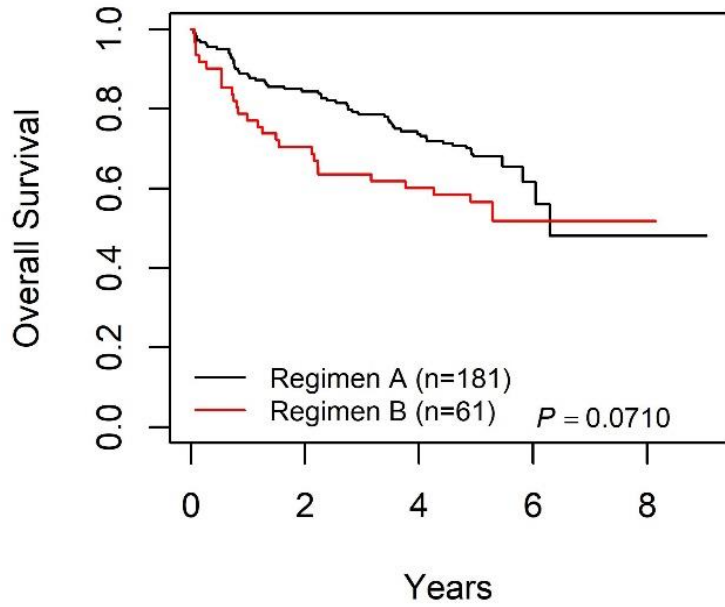


**Figure S4**

**A**



**B**



**Table S1** – Chemotherapy Details

**INDUCTION 1:**

Week	1	2	3	4	5
PRED	X.....				
VCR	X	X	X	X	
PEG-ASP	X	X	X	X	
DOXO	X				
IT ARAC/IT MTX	X <sup>AraC</sup>		X		X
(ITT)*	(X)*	(X)*	(X)*	(X)*	(X)*

Weeks 1-5:

Prednisone – 40 mg/m<sup>2</sup>/day PO divided TID x 28 days  
**Vincristine – 1.5 mg/m<sup>2</sup> (max 2 mg) vs. 2 mg/m<sup>2</sup> (max 2.5 mg) IV**  
Pegaspargase – 2500 units/m<sup>2</sup> IM  
Doxorubicin – 60 mg/m<sup>2</sup> IV  
Intrathecal ARAC – (dose by age) for CNS-negative ONLY on Day 1 only  
Intrathecal Methotrexate – (dose by age) for CNS-negative ONLY on Days 15, 29  
\*Intrathecal Triples (MTX/HC/ARAC) for CNS-positive ONLY Days 1, 8, 15, 22, 29

**INDUCTION 2:** \*(CNS-positive patients receive INDUCTION 3 before INDUCTION 2)

Week	6	7	8	9	10
CPM	XXXXX				
ETOP	XXXXX				
G-CSF		X.....			
HD MTX/LEUC				X	
IT MTX (ITT)*	X			X	
^Testicular XRT	(^X...)				

Weeks 6-10:

Cyclophosphamide – 440 mg/m<sup>2</sup>/day IV x 5 days  
Etoposide – 100 mg/m<sup>2</sup>/day IV x 5 days  
GCSF – 5 mcg/kg/day SubQ/IV. daily  
Methotrexate – 5 grams/m<sup>2</sup> IV over 24 hours  
Leucovorin – 15 mg/m<sup>2</sup> IV/PO q6 hrs x min. 3 doses starting @ hr 42  
Intrathecal MTX – dose by age \*(ITT for CNS-positive only)  
^Testicular Relapse with Persistent Disease: XRT – 2400 cGy to be completed prior to HDMTX

**INDUCTION 3:** \*(CNS-positive patients receive INDUCTION 3 before INDUCTION 2)

Week	11	12	13	14	15
HD ARAC	XXXX	XXXX			
L-ASP	X	X			
G-CSF			X.....		

Weeks 11-15:

Cytarabine – 3000 mg/m<sup>2</sup> IV q12 hrs x 4 doses  
*E. coli* asparaginase – 6000 International units/m<sup>2</sup> IM  
GCSF – 5 mcg/kg SubQ/IV daily

**INTENSIFICATION 1:** (for those without a matched family donor for SCT)

Week	16	17	18	19	20	21	22	23	24	25
26										
27										
HD MTX/LEUC	X		X			X			X	
MP	X....		X....			X....			X....	
VCR	X		X			X			X	
ETOP	X			X			X			X
CPM	X			X			X			X
IT MTX (ITT)*		X			X			X		

Weeks 16-27:

Methotrexate – 5 grams/m<sup>2</sup> IV over 24 hours  
Leucovorin – 15 mg/m<sup>2</sup> IV/PO q6 hrs x min. 3 doses starting @ hr 42  
Mercaptopurine - 50 mg/m<sup>2</sup> PO daily x 5 days  
**Vincristine – 1.5 mg/m<sup>2</sup> (max 2 mg) vs. 2 mg/m<sup>2</sup> (max 2.5 mg) IV**  
Etoposide - 300 mg/m<sup>2</sup> IV  
Cyclophosphamide - 500 mg/m<sup>2</sup> IV  
Intrathecal MTX – dose by age \*(ITT for CNS-positive)

**REINDUCTION:**

Week	28	29	30	31	32
DEX	XXXXXXX		XXXXXXX		
VCR	X	X	X		
PEG-ASP	X		X		
DOXO	X	X	X		
IT MTX (ITT)*	X			X	

Weeks 28-32: Dexamethasone – 10 mg/m<sup>2</sup>/day PO divided BID days 1-7,15-21 (all ages)  
**Vincristine – 1.5 mg/m<sup>2</sup> (max 2 mg) vs. 2 mg/m<sup>2</sup> (max 2.5 mg) IV**  
Pegaspargase - 2500 International units/m<sup>2</sup> IM  
Doxorubicin - 25 mg/m<sup>2</sup> IV  
Intrathecal MTX – dose by age \*(ITT for CNS-positive)

**INTENSIFICATION 2: (6-week cycle repeated 4 times = 24 weeks)**

Week	33	34	35	36	37	38.....	51	52	53	54	55
56											
HD ARAC	XXXX						XXXX				
PEG-ASP	X							X			
G-CSF		X...						X...			
HD MTX/LEUC				X						X	
MP				X⑤						X⑤	
VCR				X	X					X	X
ETOP					X						X
CPM					X						X
IT MTX (ITT)*						X					

Weeks 33-56: Cytarabine – 3000 mg/m<sup>2</sup> IV q12 x 4 doses  
Pegaspargase - 2500 International units/m<sup>2</sup> IM  
GCSF – 5 mcg/kg/day SubQ/IV daily  
Methotrexate – 5 grams/m<sup>2</sup> IV over 24 hours  
Leucovorin – 15 mg/m<sup>2</sup> IV/PO q6 hrs x min. 3 doses starting @ hr 42  
Mercaptopurine - 50 mg/m<sup>2</sup> PO daily x 5  
**Vincristine – 1.5 mg/m<sup>2</sup> (max 2 mg) vs. 2 mg/m<sup>2</sup> (max 2.5 mg) IV**  
Etoposide - 300 mg/m<sup>2</sup> IV  
Cyclophosphamide - 500 mg/m<sup>2</sup> IV  
Intrathecal MTX – dose by age \*(ITT for CNS-positive only)

**MAINTENANCE: (10-week cycle repeated 5 times = 50 weeks)**

Week	57	58	59	60	61	62	63	64	65	66.....	106
DEX	X....										
MP	X.....										
MTX	X*	X	X	X	X	X					
(*CNS+ only)											
IT MTX <sup>!</sup>	X <sup>!</sup>										
VCR							X	X	X	X	
CPM							X	X	X	X	
CNS XRT*	X*...										

Weeks 57-106: Dexamethasone – 10 mg/m<sup>2</sup>/day PO divided BID x 5 days  
**Vincristine – 1.5 mg/m<sup>2</sup> (max 2 mg) vs. 2 mg/m<sup>2</sup> (max 2.5 mg) IV**  
Cyclophosphamide – 300 mg/m<sup>2</sup> IV  
Mercaptopurine – 75 mg/m<sup>2</sup> PO nightly  
Methotrexate – 40 mg/m<sup>2</sup> PO qWk except on weeks of IT MTX \*(give for CNS-pos)  
! CNS-negative only: Intrathecal MTX – dose by age q10 weeks  
\* CNS-positive only: Cranial Radiation – 1800 cGy at beginning of Maintenance Cycle 1

**Table S2 – Deaths due to toxicity**



<b>Stratum</b>	<b>Phase of Therapy</b>	<b>Reported etiology / inciting organism</b>
BM	Induction-1	<i>Methicillin-resistant Staphylococcus aureus (MRSA)</i>
Combined BM/CNS	Induction-3	<i>Clostridium septicum + Staphylococcus aureus</i>
BM	Induction-1	<i>E.coli + Candida species (pneumonia / sepsis)</i>
CNS	Intensification-2	<i>Pseudomonas aeruginosa</i>
BM	Induction-3	<i>Rhizopus species</i>
BM	Induction-1	<i>MRSA + Candida Tropicalis</i>
BM	Intensification-2	<i>Influenza A (H1N1) + Aspergillus</i>
BM	Induction-1	<i>Candida albicans</i>
BM	Induction-3	<i>Candida tropicalis</i>
BM	Induction-1	<i>Klebsiella oxytoca + Streptococcus species + Pseudomonas aeruginosa</i>
BM	Induction-1	<i>Unknown organism (Pansinusitis / periorbital cellulitis / cavernous sinus thrombosis / internal carotid artery occlusion / multiple cerebral septic infarcts / otitis media)</i>
BM	Intensification-2	<i>Escherichia coli</i>
BM	Intensification-2	<i>Unknown organism (Multi-organ failure / sepsis)</i>
Combined BM/CNS	Induction-1	<i>Rhizopus species (mucormycosis)</i>
Combined BM/CNS	Induction-1	<i>Streptococcus mitis + Aspergillus species</i>
BM	Intensification-2	<i>Pseudomonas species (perirectal abscess / sepsis)</i>
BM	Intensification-2	<i>Pseudomonas aeruginosa</i>
Combined BM/CNS	Induction-1	<i>Methicillin Resistant Staphylococcus Aureus</i>

BM: Bone Marrow

CNS: Central Nervous System